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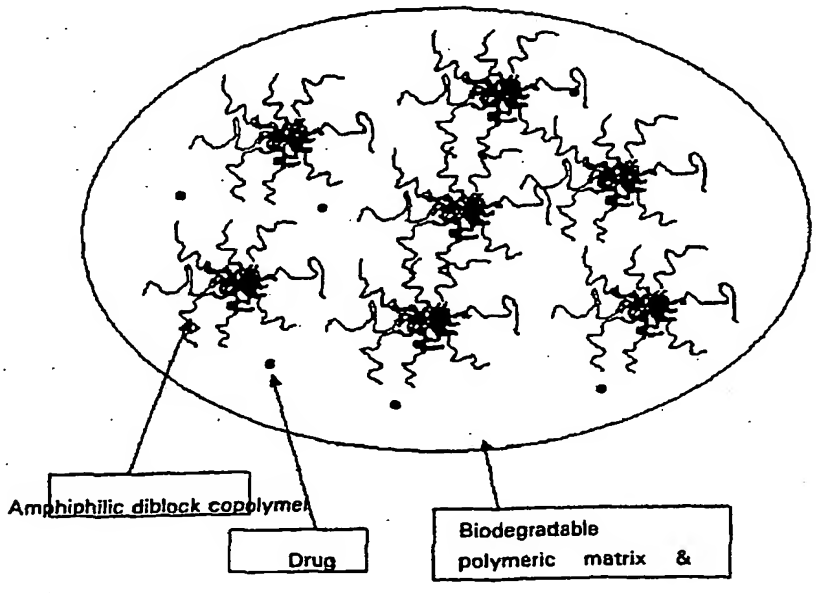

(57) Abstract: A composition for the sustained delivery of a drug comprising an amphiphilic diblock copolymer; a poorly water-soluble drug; a biodegradable polymer; and liquid poly(ethylene glycol) or functional derivatives thereof and a process for preparing the composition are disclosed. When administered into a particular body site, the composition forms an implant and the drug and polymeric micelles containing the same are slowly released from the implant to maintain a constant drug concentration for an extended period of time.

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COMPOSITIONS FOR SUSTAINED DELIVERY OF HYDROPHOBIC DRUGS AND PROCESS FOR THE PREPARATION THEREOF

TECHNICAL FIELD

The present invention relates to a composition for the sustained delivery of a hydrophobic drug and to a process for preparing the same. More specifically, the present invention relates to a liquid composition for the sustained delivery of a hydrophobic drug comprising: i) an amphiphilic diblock copolymer; ii) a hydrophobic drug; iii) a biodegradable polymer; and iv) liquid polyethylene glycol or derivatives thereof. The amphiphilic diblock copolymer forms polymeric micelles in the liquid polyethylene glycol and the hydrophobic drug is physically trapped within the micelles. Further the biodegradable polymer forms matrices in the liquid polyethylene glycol such that the drug containing micelles in the polyethylene glycol are contained within the biodegradable polymer matrices. Therefore, when injected into a living body, the composition forms a polymeric implant comprising the drug containing micelles within the polymeric matrices. The micelles and drug are gradually released from the matrices and the drug is then slowly released from the micelles in a controlled manner providing for a constant drug concentration *in vivo* for an extended period of time. The diblock copolymer, biodegradable polymer and polyethylene glycol decompose into materials harmless to the human body.

BACKGROUND ART

Numerous studies regarding drug delivery systems have been conducted with a variety of drugs and methods in an effort to maximize the efficacy and effects of drugs and minimize the side effects of drugs by efficient administration means and controlling the rate of drug release.

Biocompatible, biodegradable polymers have been widely used in the medical field as surgical sutures, tissue regenerative induction membranes, protective membranes for the treatment of wounds, and drug delivery systems. Among biodegradable polymers, polylactide (PLA), polyglycolide (PGA) and a copolymer (PLGA) of lactide and glycolide, are all commercially available. They have good biocompatibility and are decomposable in the body to harmless materials such as carbon dioxide, water, *etc*.

One example of a biodegradable polymeric drug delivery system is a system wherein a drug is contained in a biodegradable polymer matrix. These systems have the disadvantage of having to be surgically implanted. In the form of injectable drug delivery systems, polymeric microspheres and nanospheres are known in the art. However, those systems have disadvantages in that they require special preparation methods. In addition, since the biodegradable polymers used can only be dissolved in organic solvents, preparation requires the use of organic solvents harmful to the human body and therefore any residual solvent remaining after preparation of the microspheres must be completely removed. Furthermore, some drugs, such as polypeptides and proteins, may lose their physiological activity after contacting organic solvents.

Most drugs, after administration, must have a constant plasma concentration in order to provide for the desired pharmacological effects. In particular, drugs with short half-lives must be administered frequently to achieve effective plasma concentrations. For such drugs, sustained delivery formulations from which the drugs are slowly released to continuously provide their pharmacological effects, have been developed.

Many important drugs are hydrophobic and have limited solubility in water. In order to attain the expected therapeutic effect from such drugs it is usually required that a solubilized form of the drug be administered to a patient. Therefore, solubilization of a poorly water soluble drug is key technology in the preparation of a formulation for oral or

parenteral, especially intravenous, administration of the drug. Common methods used for solubilization of poorly water soluble drugs are: i) dissolving the drug in a co-solvent of a water-miscible organic solvent and water; ii) modifying the drug to its salt form which is soluble in water; iii) forming a soluble drug-complex using a complexing agent; iv) introducing a hydrophilic group into a drug molecule; v) micellizing the drug in an aqueous medium with a surfactant, and vi) dispersing the drug in water to form emulsions, liposomes, nanoparticles and the like [S. Sweetana, *et al.*, Solubility Principles and Practices for Parenteral Drug Dosage Form Development, PDA J. Pharm. Sci. & Tech. 60 (1996) 330-342].

U.S. Patent No. 5,543,158 discloses a nanoparticle, wherein a drug is entrapped therein, formed of a block copolymer consisting of a hydrophilic polyethylene glycol block and a hydrophobic poly(lactide-co-glycolide) block. The nanoparticle has a hydrophilic outer shell that can decrease uptake of the drug by the reticuloendothelial system thus allowing it to remain in the systemic circulation for an extended period of time. However, in order to manufacture the formulation, organic solvents harmful to the human body have to be used in order to dissolve the drugs and the polymers. Furthermore, the drugs are completely exhausted from the blood within several days because they are intravascularly injected.

X. Zhang *et al.* reported that a polymeric micelle prepared with a diblock copolymer of poly(lactic acid) and monomethoxy poly(ethylene glycol) was useful as a carrier of paclitaxel [X. Zhang *et al.*, Int. J. Pharm. 132 (1996) 195-206], and Shin *et al.* disclose a solubilization method for indomethacin using a diblock copolymer of poly(ethylene glycol) and polycaprolactone [I. Gyun Shin *et al.*, J. Contr. Rel. 51 (1998) 13-22]. In these methods, a poorly water soluble drug is incorporated in a polymeric micelle, wherein the polymers are biocompatible and biodegradable. According to their methods, a drug and a block copolymer are dissolved together in an organic solvent, especially in a water-miscible organic solvent such as tetrahydrofuran or dimethyl

formamide. The polymeric micelles are prepared by dialyzing the solution in water first and then freeze-drying the aqueous micellar solution. Alternatively, a solution of a polymer and drug in a water-miscible organic solvent, acetonitrile, is prepared. The organic solvent is slowly evaporated to give a homogeneous drug-polymer matrix and the matrix is then dispersed in an aqueous medium at ca. 60°C to form the polymeric micelles.

Implants can be directly applied to a particular body site rather than being intravascularly injected. For example, US Patent No. 5,869,079 discloses an implant comprising the poorly water-soluble drug dexamethasone, a copolymer of lactic acid and glycolic acid, and hydroxypropyl methylcellulose. In addition, US Patent No. 6,004,573 discloses that a PLGA-PEG-PLGA triblock copolymer made up of hydrophobic poly(lactide-co-glycolide) (PLGA) blocks and a hydrophilic polyethylene glycol (PEG) block can be used as an implant for effectively delivering poorly water-soluble drugs. However, the above formulations fail to provide for effective plasma concentrations of poorly water-soluble drugs due to their extremely low solubility in body fluids. Thus, a composition for use as an implant that can be prepared by a simple procedure, and which releases the hydrophobic drug over an extended period of time and is administered by a single injection and then decomposes into materials harmless to human body, is needed.

DISCLOSURE OF THE INVENTION

The present invention provides a composition for the sustained delivery of a hydrophobic drug that is capable of forming an implant when administered into a particular body site.

The present invention also provides a composition for the sustained delivery of a hydrophobic drug that forms an implant when administered into a particular body site and the drug and polymeric micelles containing the drug are slowly released, *in vivo*, from the implant.

One aspect of the present invention relates to a composition for the sustained delivery of a poorly water-soluble drug comprising: i) an amphiphilic diblock copolymer; ii) a poorly water-soluble drug; and iii) a biodegradable polymer, dispersed or suspended in liquid poly(ethylene glycol) or a suitable derivative thereof.

According to the present invention, the amphiphilic diblock copolymer forms polymeric micelles in the liquid polyethylene glycol and the poorly water-soluble drug is trapped within the polymeric micelles. In addition, when administered into the body, the biodegradable polymer develops into an implant by forming matrices in the liquid polyethylene glycol. The drug and polymeric micelles containing the drug are slowly released *in vivo* from the implant matrices over sustained periods of time and the polymers then decompose into materials harmless to the human body.

The amphiphilic diblock copolymer in the present invention is preferably a block copolymer of a hydrophilic poly(alkylene glycol) block and a hydrophobic biodegradable polymer block dispersed or suspended in a poly(ethylene glycol) matrix, or its derivatives. The term poly(ethylene glycol) or PEG, as used herein, shall also be deemed to include derivatives of PEG unless otherwise specifically stated. Such derivatives will be more specifically described in the disclosure that follows. Since only the hydrophilic component block, not the hydrophobic component block, of the copolymer has an affinity or attraction for the poly(ethylene glycol) matrix, the block copolymer forms a core-shell structure wherein the hydrophobic biodegradable polymer block occupies the inner core and the hydrophilic poly(alkylene glycol) block forms the outer shell in the poly(ethylene glycol) medium. In addition, the biodegradable polymer employed in the present invention forms matrices in liquid polyethylene glycol and controls the release rate of the hydrophobic drug and polymeric micelles which contain the hydrophobic drug.

The content of the amphiphilic diblock copolymer is preferably within the range of

3 to 70% by weight and more preferably of 5 to 50% by weight, based on the total weight of the composition. The drug content is within the range of 0.1 to 50% by weight and preferably 1 to 30% by weight, based on the weight of the amphiphilic diblock copolymer. The content of the biodegradable polymer is within the range of 5 to 80% by weight and preferably 10 to 70% by weight, based on the total weight of the composition. The molecular weight of the biodegradable polymer is within the range of 500 to 50,000 Daltons and is preferably from 1,000 to 30,000 Daltons. The content of liquid polyethylene glycol employed in the present invention is within the range of 5 to 80% by weight and is preferably from10 to 60% by weight, based on the total weight of the composition.

The composition of the present invention forms implants when administered into a particular body site, and the drug and polymeric micelles containing the same are slowly released therefrom. Therefore, a constant concentration of the drug is kept at the administration site as well as in the circulation thereby achieving excellent pharmacological effects. Also, no organic solvent harmful to the human body is involved in the composition or the preparation process thereof. Moreover, the polymers employed in the present invention are safely degraded into products harmless to the human body and then excreted. The present invention is described in detail hereinafter.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a schematic representation of the composition of the present invention;

Fig. 2 schematically illustrates drug release from a tissue implant formed when the composition of the present invention is injected into the body;

Fig. 3 illustrates the results of *in vitro* drug release tests for the composition of the present invention;

Fig. 4 illustrates the anticancer activity of the paclitaxel-containing composition of the present invention against human ovarian cancer; and,

Fig. 5 illustrates the anticancer activity of the paclitaxel-containing composition of

the present invention against human prostatic carcinoma.

BEST MODE FOR CARRYING OUT THE INVENTION

The present invention relates to a composition for the sustained delivery of a poorly water-soluble drug comprising: i) an amphiphilic diblock copolymer; ii) a poorly water-soluble drug; and iii) a biodegradable polymer, dispersed or suspended in liquid poly(ethylene glycol). The composition of the present invention forms a polymeric implant when injected into a living body, and contains a poorly water soluble drug and drug-containing micelles which slowly release the drug and the drug containing micelles over a prolonged period of time and is then decomposed into materials harmless to the human body.

The block copolymer portion of such compositions has a core-shell structure wherein the hydrophobic biodegradable polymer block occupies the inner core and the hydrophilic poly(alkylene glycol) block forms the outer shell in the hydrophilic liquid poly(ethylene glycol) matrix or medium. The poly(ethylene glycol) functions as a dispersant to facilitate water solubility and the block copolymer portion of the composition forms a micellular structure in body fluids or in an aqueous medium. When a poorly water soluble drug is added to the composition, it is contained within the inner hydrophobic core. Accordingly, a pharmaceutical formulation containing the composition of the present invention is capable of effectively solubilizing a poorly water soluble drug in a body fluid or in an aqueous medium by forming a micelle, wherein the drug is entrapped in the core of the micelle. In addition, the biodegradable polymer employed in the present invention forms matrices in liquid polyethylene glycol which controls the release rate of the hydrophobic drug and polymeric micelles containing the hydrophobic drug, from the implant site into the body.

In summary, the present invention is a combination of an amphiphilic diblock

copolymer and a biodegradable polymer, as defined herein, suspended in a liquid poly(ethylene glycol) medium. The amphiphilic diblock copolymer comprises a hydrophilic poly(alkylene glycol) component and a hydrophobic biodegradable polymer component. The poly(ethylene glycol) medium facilitates the dispersion of the diblock copolymer which forms a polymeric micelle. When a poorly water soluble drug is added to the composition, the drug is solubilized by incorporating the drug into the inner core of the micelle. The composition of the present invention forms a polymeric implant when injected into a living body, from which the drug and the drug-containing micelles are slowly released over a prolonged period of time and the implant is then decomposed into materials harmless to the human body and excreted.

The polyalkylene glycol suitable for the hydrophilic component of the amphiphilic diblock copolymer of the present invention is a member selected from the group consisting of polyethylene glycol, monoalkoxy polyethylene glycol, or monoacyloxy polyethylene glycol wherein the molecular weight of the polyalkylene glycol is preferably within the range of 500~20,000 Daltons, and more preferably within the range of 1,000~15,000 Daltons. The content of the hydrophilic component of the amphiphilic diblock copolymer is within the range of 30~80wt%, preferably 40~70wt%, based on the total weight of the block copolymer.

The hydrophobic biodegradable polymer component of the amphiphilic diblock copolymer of the present invention is a member selected from the group consisting of polylactides, polycaprolactone, copolymers of lactide and glycolide, copolymers of lactide and caprolactone, copolymers of lactide and 1,4-dioxan-2-one, polyorthoesters, polyanhydrides, polyphosphazines, poly(amino acid)s and polycarbonates. Preferably, the hydrophobic biodegradable polymer component of the copolymer of the present invention is a member selected from the group consisting of polylactides, polycaprolactone, a copolymer of lactide and glycolide, a copolymer of lactide and caprolactone, and a copolymer of lactide and 1,4-dioxan-2-one. The molecular weight of the hydrophobic

biodegradable polymer component is preferably within the range of 500~20,000 Daltons, and more preferably within the range of 1,000~15,000 Daltons.

The amphiphilic diblock copolymer of the present invention can be synthesized by polymerizing lactone type heterocyclic esters and monoalkoxypolyethylene glycols at a temperature of 80 to 130 °C using stannous octoate ($SnOct_2$) as a catalyst [E. Piskin *et al.*, Novel PDLA/PEG copolymer micelles as drug carriers, J. of Biomater. Sci. Polymer Edn. 7 (4) (1995) 359-373]. For example, they may be prepared via ring opening bulk polymerization of one of the cyclic ester monomers, such as lactide, glycolide, or 1,4-dioxan-2-one with monomethoxy poly(ethylene glycol) (mPEG) or poly (ethylene glycol) (PEG) in the presence of stannous octoate as a catalyst at 80~130°C. When the 1,4-dioxan-2-one is used as the monomer, the preferable reaction temperature is 80~110°C. When a copolymer of 1,4-dioxan-2-one and lactide is used, the 1,4-dioxan-2-one monomer is first reacted with mPEG or PEG at 100~130 °C, the lactide monomer is then slowly added to increase the degree of polymerization of 1,4-dioxan-2-one. Since the conversion of the 1,4-dioxan-2-one monomer is 50~60%, the added amount of this monomer should be more than the calculated amount when the two monomers, 1,4-dioxan-2-one and lactide, are added together. The block copolymer product is dissolved in dichloromethane or acetone, precipitated in diethyl ether, hexane, pentane, or heptane, followed by drying.

The liquid poly(ethylene glycol) or its derivatives, used as a dispersion medium for the composition of the present invention, have high attraction for the hydrophilic component of the diblock copolymer and preferably, have melting temperature of below about 40 °C, and molecular weights of 100~3,000 Daltons and more preferably 200~2,000 Daltons. The term "liquid" used herein is defined as the liquid phase at the temperature of 50 °C. Accordingly, the liquid polyethylene glycol employed in the present invention may be one or more selected from the group consisting of polyethylene glycol, and alkyl or allyl derivatives thereof, each of which is liquid at 50 °C.

As shown in Fig. 1, the biodegradable polymer employed in the present invention forms matrices in liquid polyethylene glycol and controls the rate of release of the drug and polymeric micelles containing the same. The biodegradable polymer employed in the present invention should be biocompatible, be degradable into products harmless to the human body after a given time *in vivo*, and be soluble or uniformly dispersible in liquid polyethylene glycol of low molecular weight. Examples of the biodegradable polymer include polylactide, polycaprolactone, poly(lactide-co-glycolide) and mixtures thereof. The content of the biodegradable polymer is within the range of 5 to 80% by weight and preferably of 10 to 70% by weight, based on the total weight of the composition. The molecular weight of the biodegradable polymer is within the range of 500 to 50,000 Daltons and is preferably from 1,000 to 30,000 Daltons.

The content of the amphiphilic diblock copolymer is preferably within the range of 3 to 70% by weight and more preferably from 5 to 50% by weight, based on the total weight of the composition. The drug content is within the range of 0.1 to 50% by weight and preferably from 1 to 30% by weight, based on the weight of the amphiphilic diblock copolymer. The content of the biodegradable polymer is within the range of 5 to 80% by weight and preferably from 10 to 70% by weight, based on the total weight of the composition. The content of liquid polyethylene glycol employed in the present invention is within the range of 5 to 80% by weight and preferably from 10 to 60% by weight, based on the total weight of the composition.

When introduced into the body, the composition of the present invention forms an implant. As illustrated in Figure 2, the poorly water-soluble drugs are entrapped within the polymeric micelles formed by the amphiphilic diblock copolymer which in turn are embedded in the biodegradable polymer matrix and the liquid polyethylene glycol (PEG) medium. Therefore, the drugs and drug-containing micelles are slowly released from the polymeric micelles and from the implant thereby to provide a constant drug circulation concentration for an extended period of time. Thus the compositions of the present

invention are especially useful for the sustained delivery of poorly water soluble drugs having solubilities of less than 10mg/mL at ambient temperatures. Examples of these hydrophobic drugs include anticancer agents, antiinflammatory agents, antifungal agents, antiemetics, antihypertensive agents, sex hormones, and steroids. Typical examples of these hydrophobic drugs are: anticancer agents such as paclitaxel, docetaxel, camptothecin, doxorubicin, daunomycin, cisplatin, 5-fluorouracil, mitomycin, methotrexate, and etoposide; antiinflammatory agents such as indomethacin, ibuprofen, ketoprofen, flubiprofen, dichlofenac, piroxicam, tenoxicam, naproxen, aspirin, and acetaminophen; antifungal agents such as itraconazole, ketoconazole and amphotericin; sex hormons such as testosterone, estrogen, progesterone, and estradiol; steroids such as dexamethasone, prednisolone, betamethasone, triamcinolone acetonide and hydrocortisone; antihypertensive agents such as captopril, ramipril, terazosin, minoxidil, and parazosin; antiemetics such as ondansetron and granisetron; antibiotics such as metronidazole, and fusidic acid; cyclosporines; prostaglandins; and biphenyl dimethyl dicarboxylic acid.

The rate of release of a drug and of the polymeric micelles containing the same, depends on the composition of the biodegradable polymer and the molecular weight and content thereof, because the degradation rate depends on the kind of polymer employed and the viscosity of the matrix depends on the molecular weight and content of the polymer employed.

Since the composition of the present invention contains a biocompatible polymer which is degradable after a given time into products that are harmless to the human body and is excreted from the body, the drug release rate can be controlled by adjusting the content of each component. The composition forms implants when injected into a particular body site, the drug and the polymeric micelles containing the same, are slowly released from the implants, thereby keeping a constant concentration of the drug at the implantation site as well as in the circulation for an extended period of time. Therefore, the composition of the present invention can provide for excellent pharmacological effects.

That is, as shown in the following Example 19 (drug release test), in a composition without the amphiphilic diblock copolymer (Comparative Example 1), only an extremely small amount of the drug is released into an aqueous medium. In a composition without the biodegradable polymeric matrix (Comparative Example 2), the drug is completely released into the aqueous medium within 24 hours. By contrast, the present composition can control the release of the drug and the polymeric micelles containing the same, by adjusting the content of each component. Therefore, the present composition provides for a constant concentration of the drug for an extended period of time.

The composition of the present invention may be prepared as follows. An amphiphilic diblock copolymer, and a poorly water-soluble drug are mixed in liquid polyethylene glycol and stirred to prepare a polymeric micellar composition (Composition A) containing the poorly water-soluble drug entrapped therein. In the above process, the stirring is carried out, preferably at a temperature of 40 to 80 °C, for 30 to 60 minutes. A biodegradable polymer is dissolved or dispersed in liquid polyethylene glycol to prepare Composition B. Then, Composition A is mixed with Composition B and stirred to prepare a composition for the sustained delivery of a drug of the present invention. In the above process the stirring is carried out, preferably at a temperature of 40 to 80 °C, for 1 to 2 hours.

The composition of the present invention may be injected into a particular site of the human body by means of a syringe or catheter. The polymers contained in the present composition are safe in that the United States Food and Drug Administration (FDA) has allowed them for *in vivo* use. The polymers have the additional advantage in that they are hydrolyzed into products readily excreted from the body.

While the following preparations and examples are provided for the purpose of illustrating certain aspects of the present invention, they are not to be construed as limiting the scope of the appended claims.

EXAMPLES

Synthesis of Amphiphilic Diblock copolymer

Preparation 1: mPEG-PLA (MW 2,000-1,800)

25 g of methoxypolyethylene glycol (mPEG, MW=2,000) and 25 g of D,L-lactide recrystallized from ethyl acetate were added to a round-bottomed flask equipped with a pedal stirrer. Thereto was added 0.25 g of stannous octoate ($SnOct_2$) dissolved in 5 ml of toluene. The flask was then heated to 120 °C in an oil bath to evaporate excess toluene. Subsequently, the reaction was performed under reduced pressure (25 mmHg) for 6 hours. The resulting product was dissolved in chloroform. The solution was slowly added to cold diethyl ether (4 °C) to precipitate the formed polymer. The polymer was purified by repeating the dissolution-precipitation process twice and was then dried in a vacuum oven (0.1 mmHg) for 24 hours. The molecular weight of the copolymer (mPEG-PLA) was identified by Nuclear Magnetic Resonance (NMR) Spectroscopy.

Preparation 2: mPEG-PLA (MW 3,400-2,500)

According to substantially the same method as in Preparation 1, a copolymer (mPEG-PLA) was prepared using 25 g of methoxypolyethylene glycol (mPEG, MW=3,400), 20 g of D,L-lactide, and 0.20 g of stannous octoate, and the molecular weight of the copolymer was identified.

Preparation 3: mPEG-PLA (MW 5,000-4,000)

According to substantially the same method as in Preparation 1, a copolymer (mPEG-PLA) was prepared using 25 g of methoxypolyethylene glycol (mPEG, MW=5,000), 22 g of D,L-lactide, and 0.22 g of stannous octoate, and the molecular weight of the copolymer was identified.

Preparation 4: mPEG-PLA (MW 8,000-6,000)

According to substantially the same method as in Preparation 1, a copolymer

(mPEG-PLA) was prepared using 25 g of methoxypolyethylene glycol (mPEG, MW=8,000), 20 g of D,L-lactide, and 0.20 g of stannous octoate, and the molecular weight of the copolymer was identified.

Preparation 5: mPEG-PCL (MW 5,000-4,000)

According to substantially the same method as in Preparation 1, a copolymer (mPEG-PCL) was prepared using 25 g of methoxypolyethylene glycol (mPEG, MW=5,000), 20 g of ε-caprolactone, and 0.20 g of stannous octoate, and the molecular weight of the copolymer was identified.

Preparation 6: mPEG-PLGA (MW 5,000-4,000, LA/GA=7/3)

According to substantially the same method as in Preparation 1, a copolymer (mPEG-PLGA) was prepared using 25 g of methoxypolyethylene glycol (mPEG, MW=5,000), 15 g of D,L-lactide, 7 g of glycolide and 0.22 g of stannous octoate, and the molecular weight of the copolymer was identified.

Preparation 7: mPEG-PLDO (MW 5,000-4,000, LA/DO=7/3)

According to substantially the same method as in Preparation 1, a copolymer (mPEG-PLDO) was prepared using 25 g of methoxypolyethylene glycol (mPEG, MW=5,000), 15 g of D,L-lactide, 7 g of 1-*p*-dioxanone and 0.22 g of stannous octoate, and the molecular weight of the copolymer was identified.

Preparation of Biodegradable Polymer Controlling Release Rate

Preparation 8: PLA (MW 4,000)

30 g of lactic acid was added to a round-bottomed flask equipped with a pedal stirrer. Thereto was added 0.15 g of antimony oxide (Sb_2O_3). The flask was equipped with a distillation tube, and the temperature was slowly increased. The reaction was performed at 160 °C for 10 hours. Subsequently, the reaction was further performed under reduced pressure (25 mmHg) for an additional 6 hours. The resulting product was dissolved in

chloroform. The solution was slowly added to cold diethyl ether (4 °C) to precipitate the formed polymer. The polymer was purified by repeating the dissolution-precipitation process twice and then the polymer was dried in a vacuum oven (0.1 mmHg) for 24 hours. The molecular weight of the polymer (PLA) was identified by Nuclear Magnetic Resonance (NMR) Spectroscopy.

Preparation 9: PLGA (MW 4,000, LA/GA=7/3)

According to substantially the same method as in Preparation 8, a PLGA polymer was prepared using 21 g of lactic acid and 9 g of glycolic acid, and the molecular weight of the copolymer was identified.

Preparation of Drug Composition

Example 1: Paclitaxel containing composition

In a round-bottomed flask equipped with a pedal stirrer were mixed 90 mg of the amphiphilic diblock copolymer (mPEG-PLA) prepared in Preparation 1, 10 mg of paclitaxel as a poorly water-soluble drug and 100 mg of a liquid polyethylene glycol (PEG, MW 300). Then, the mixture was stirred at 60 °C for 30 minutes to prepare Composition A. According to the same method as above, 100 mg of polylactide (PLA, MW 4,000) as a biodegradable polymer that forms matrices, was dissolved in 100 mg of the same polyethylene glycol used to prepare Composition B. Composition A was mixed with Composition B and stirred at 60 °C for 1 hour to prepare a transparent viscous liquid composition.

Examples 2 to 18:

Poorly water-soluble drug containing compositions were prepared using the ingredients and the contents as listed in Table 1 below, according to substantially the same method as in Example 1.

Comparative Examples 1 and 2:

Poorly water-soluble drug containing compositions were prepared using the ingredients and the contents as listed in Table 1 below.

Table 1

	Amphiphilic diblock copolymer	Drug	PEG	Polymeric matrix*
Example 1	mPEG-PLA(MW 2,000-1,800) 90 mg	Paclitaxel 10 mg	PEG(MW 300) 200 mg	PLA 100 mg
Example 2	mPEG-PLA(MW 2,000-1,800) 90 mg	Paclitaxel 10 mg	PEG(MW 300) 300 mg	PLA 100 mg
Example 3	mPEG-PLA(MW 2,000-1,800) 90 mg	Paclitaxel 10 mg	PEG(MW 600) 400 mg	PLA 300 mg
Example 4	mPEG-PLA(MW 2,000-1,800) 90 mg	Paclitaxel 10 mg	PEG(MW 600) 400 mg	PLA 600 mg
Example 5	mPEG-PLA(MW 3,400-2,500) 90 mg	Paclitaxel 10 mg	PEG(MW 300) 400 mg	PLA 300 mg
Example 6	mPEG-PLA(MW 3,400-2,500) 90 mg	Paclitaxel 10 mg	PEG(MW 300) 400 mg	PLA 600 mg
Example 7	mPEG-PLA(MW 3,400-2,500) 90 mg	Paclitaxel 10 mg	PEG(MW 300) 400 mg	PLA 900 mg
Example 8	mPEG-PLA(MW 3,400-2,500) 90 mg	Paclitaxel 10 mg	PEG(MW 300) 400 mg	PLA 1.200 mg
Example 9	mPEG-PLA(MW 3,400-2,500) 90 mg	Paclitaxel 10 mg	PEG(MW 300) 600 mg	PLA 1,200 mg
Example 10	mPEG-PLA(MW 3,400-2,500) 90 mg	Paclitaxel 10 mg	PEG(MW 600) 400 mg	PLA 600 mg
Example 11	mPEG-PLA(MW 3,400-2,500) 90 mg	Paclitaxel 10 mg	PEG(MW 800) 400 mg	PLA 600 mg
Example 12	mPEG-PLA(MW 3,400-2,500) 95 mg	Paclitaxel 5 mg	PEG(MW 300) 400 mg	PLGA 600 mg
Example 13	mPEG-PLA(MW 3,400-2,500) 90 mg	Indomethacin 10 mg	PEG(MW 300) 400 mg	PLA 600 mg
Example 14	mPEG-PLA(MW 3,400-2,500) 90 mg	Indomethacin 10 mg	PEG(MW 300) 400 mg	PLA 900 mg
Example 15	mPEG-PLA(MW 5,000-4,000) 80 mg	Indomethacin 20 mg	PEG(MW 800) 400 mg	PLA 900 mg
Example 16	mPEG-PCL(MW 5,000-4,000) 80 mg	Indomethacin 20 mg	PEG(MW 300) 400 mg	PLA 900 mg
Example 17	mPEG-PLGA(MW 5,000-4,000, LA/GA=7/3) 90 mg	Cyclosporine A 10 mg	PEG(MW 300) 400 mg	PLA 600 mg
Example 18	mPEG-PLDO(MW 5,000-4,000, LA/DO=7/3) 95 mg	Paclitaxel 5 mg	PEG(MW 300) 400 mg	PLA 300 mg
Comparative Example 1	-	Paclitaxel 10 mg	PEG(MW 600) 400 mg	PLA 300 mg
Comparative Example 2	mPEG-PLA(MW 2,000-1,800) 90 mg	Paclitaxel 10 mg	PEG(MW 600) 400 mg	-

* PLA: Poly(lactide)(MW 4,000); PLGA: Poly(lactide-co-glycolide)(MW 4,000, LA/GA=7/3)

Example 19: Drug Release Test

500 mg of each composition obtained from Examples 1 to 18 and Comparative Examples 1 and 2 were added to a capped test tube. Thereto was then added 15 ml of physiological saline. The composition solidified at the bottom was transferred into a chamber at 37 °C. The physiological saline was completely refreshed at regular intervals. An aqueous solution containing the released drug was centrifuged and the drug was extracted from the supernatant with methylene chloride. This solution was dried and the product was redissolved in a 40% aqueous acetonitrile solution. The concentration of the drug was then measured by HPLC. The results are shown in the following Table 2 and Fig. 3.

Table 2

	Cumulative Release Rate (%)						
	0 day	1 day	2 days	3 days	5 days	7 days	10 days
Example 1	0	33	40	54	65	72	85
Example 2	0	36	47	57	68	76	90
Example 3	0	31	40	51	62	70	82
Example 4	0	23	33	45	53	65	70
Example 5	0	25	36	45	57	68	78
Example 6	0	21	35	42	48	57	65
Example 7	0	18	28	37	42	49	53
Example 8	0	17	24	33	38	42	45
Example 9	0	18	30	40	45	53	57
Example 10	0	21	31	42	47	57	62
Example 11	0	20	31	40	47	55	60
Example 12	0	23	34	46	51	62	69
Example 13	0	23	33	45	55	65	71
Example 14	0	17	31	38	47	53	58
Example 15	0	17	25	33	38	45	50
Example 16	0	18	28	35	43	49	55
Example 17	0	19	30	38	47	53	57
Example 18	0	18	31	38	49	55	60
Comparative Example 1	0	2	2	3	3	3	4
Comparative Example 2	0	100	-	-	-	-	-

As shown in Table 2 and Fig. 3, the drug release rate can be controlled depending

on the content of each ingredient in the present composition. By contrast, in a composition without an amphiphilic diblock copolymer (Comparative Example 1), almost no drug was released into the aqueous medium. Additionally, in a composition without a biodegradable polymeric matrix (Comparative Example 2), the drug was completely released into the aqueous medium within 24 hours.

Example 20: Anticancer Activity on Ovarian Cancer

In preparing animals to be used in the anticancer activity test, a piece of human ovarian cancer (SKOV-3, 3-4 mm) was xenografted onto the right side of female nude mice (Balb/c, an age of 5-6 weeks, a body weight of 19-21 g) using a 12 gauge troika. When the volume of the grafted cancer tissue grew to 300-500 mm^3, the composition prepared in Example 1, which was sterilized using a 0.22 μm filter under aseptic conditions, was injected intratumorally using a 26-gauge syringe needle. For comparison, a commercially available paclitaxel formulation, which is made by dissolving 6 mg of paclitaxel and 527 mg of Cremophor® EL in 1 ml ethanol/water (1:1, v/v), was used intravenously.

The composition of the present invention (Example 1) was injected once at a dose of 20 mg/kg (day 0). The commercial formulation was administered into the tail vein three times (once on days 0, 1 and 2) at a dose of 20 mg/kg. During administration, the cancer tissue was measured on the long and short axes at 5-day intervals. The volume of cancer tissue was calculated by the formula $\pi/6((L+W)/2)^3$ wherein W represents the length of the long axis and L represents the length of the short axis. The compositions of the administered formulations are shown in the following Table 3. The volume ratio (relative volume) of the cancer tissue upon administration and at given times after administration is shown in Fig. 4.

Table 3

	Composition	Administration route*	Dose	No. of mice
Control	-	No treatment	-	6

Vehicle	Composition of Example 1 without drug	It	-	6
Commercial Formulation (iv)	Composition of the commercial formulation	Iv	20 mg/kg×3	6
Experimental Group (it)	Composition of Example 1	it	20 mg/kg	6

* it: intratumoral, iv: intravenous

Example 21: Anticancer Activity against prostatic carcinoma

A piece of human prostatic carcinoma (PC-3, 3-4 mm) was transplanted onto the right side of male nude mice (Balb/c of 5-6 weeks, 19-21 g). The anticancer activity test was then carried out according to substantially the same method as in Example 20. The compositions of the administered formulations are shown in Table 4 below. The volume ratio (relative volume) of the cancer tissue upon administration and at given times after administration is shown in *Fig. 5*.

Table 4

	Composition	Administration route*	Dose	No. of mice
Control	-	No treatment	-	6
Vehicle	Composition of Example 1 without drug	it	-	6
Commercial Formulation (iv)	Composition of the commercial formulation	iv	20 mg/kg×3	6
Experimental Group (it)	Composition of Example 1	it	60 mg/kg	6

* it: intratumoral, iv: intravenous

As shown in Figs. 4 and 5, the paclitaxel-containing composition of the present invention exhibits much higher anticancer activity than the known formulation.

While the invention has been described with respect to the above specific embodiments, it should be recognized that various modifications and changes may be made to the invention by those skilled in the art which also fall within the scope of the

invention as defined by the appended claims.

We claim:

1. A liquid polymeric composition capable of forming a drug-containing implant in a living body for the sustained delivery of the drug comprising:

i) an amphiphilic diblock copolymer;

ii) a poorly water-soluble drug;

iii) a biodegradable polymer; and,

iv) liquid poly(ethylene glycol) or a functional derivative thereof;

wherein said composition, upon being injected into a body, forms an implant, said amphiphilic diblock copolymer forms polymeric micelles in which said poorly water-soluble drug is physically trapped and said biodegradable polymer forms matrices wherein the drug containing micelles are contained.

2. The composition according to Claim 1, wherein said amphiphilic diblock copolymer is composed of a hydrophilic polyalkylene glycol block and a hydrophobic biodegradable polymer block.

3. The composition according to Claim 2, wherein said hydrophilic polyalkylene glycol block is a member selected from the group consisting of polyethylene glycol, monoalkoxypolyethylene glycol and monoacyloxypolyethylene glycol, and said hydrophobic biodegradable polymer block is a member selected from the group consisting of polylactides, polycaprolactone, poly(lactide-co-glycolide), poly(lactide-co-caprolactone), poly(lactide-co-*p*-dioxanone), polyorthoesters, polyanhydrides, poly(amino acid) and polycarbonates.

4. The composition of Claim 3, wherein said hydrophilic polyalkylene glycol block and said hydrophobic biodegradable polymer block have molecular weights of 500 to 20,000 Daltons, respectively.

5. The composition according to Claim 1, wherein the content of said amphiphilic diblock copolymer is within the range of 3 to 70% by weight based on the total weight of the composition.

6. The composition according to Claim 1, wherein said poorly water-soluble drug is selected from the group consisting of anticancer agents, antifungal agents, steroids, anti-inflammatory agents, sex hormones, immunosuppressants, antiviral agents, anesthetics, anti-emetics and anti-histamines, having solubilities in water of 10 mg/ml or less at ambient temperatures.

7. The composition of Claim 6, wherein said poorly water-soluble drug is a member selected from the group consisting of paclitaxel, docetaxel, doxorubicin, cisplatin, carboplatin, 5-FU, etoposide, camptothecin, testosterone, estrogen, estradiol, triamcinolone acetonide, hydrocortisone, dexamethasone, prednisolone, betamethasone, cyclosporines and prostaglandins.

8. The composition according to Claim 1, wherein the content of said poorly water-soluble drug is within the range of 0.1 to 50% by weight based on the total weight of the amphiphilic diblock copolymer.

9. The composition according to Claim 1, wherein said biodegradable polymer is a polylactide, polycaprolactone or poly(lactide-co-glycolide), or a mixture thereof.

10. The composition according to Claim 1, wherein the content of the biodegradable polymer is within the range of 5 to 80% by weight based on the total weight of the composition.

11. The composition according to Claim 1, wherein said biodegradable polymer has a molecular weight of 500 to 50,000 Daltons.

12. The composition of Claim 1, wherein the content of the liquid poly(ethylene glycol) is within the range of 5 to 80% by weight based on the total weight of the composition.

13. The composition according to Claim 1, wherein said liquid poly(ethylene glycol) has a molecular weight of 100 to 3,000 Daltons.

14. The composition according to Claim 1, wherein said liquid poly(ethylene glycol) is one or more member selected from the group consisting of liquid polyethylene glycol, and alkyl and allyl derivatives thereof.

15. A process for preparing the composition according to any one of Claims 1 to 14, comprising the steps of:

i) mixing liquid polyethylene glycol or derivatives thereof, an amphiphilic diblock copolymer and a poorly water-soluble drug to form a polymeric micellar polyethylene glycol liquid composition;

ii) dissolving or dispersing a biodegradable polymer in liquid poly(ethylene glycol) or derivatives thereof to form a biodegradable polymer liquid composition; and

iii) mixing together said liquid compositions of steps i) and ii).

Fig. 1

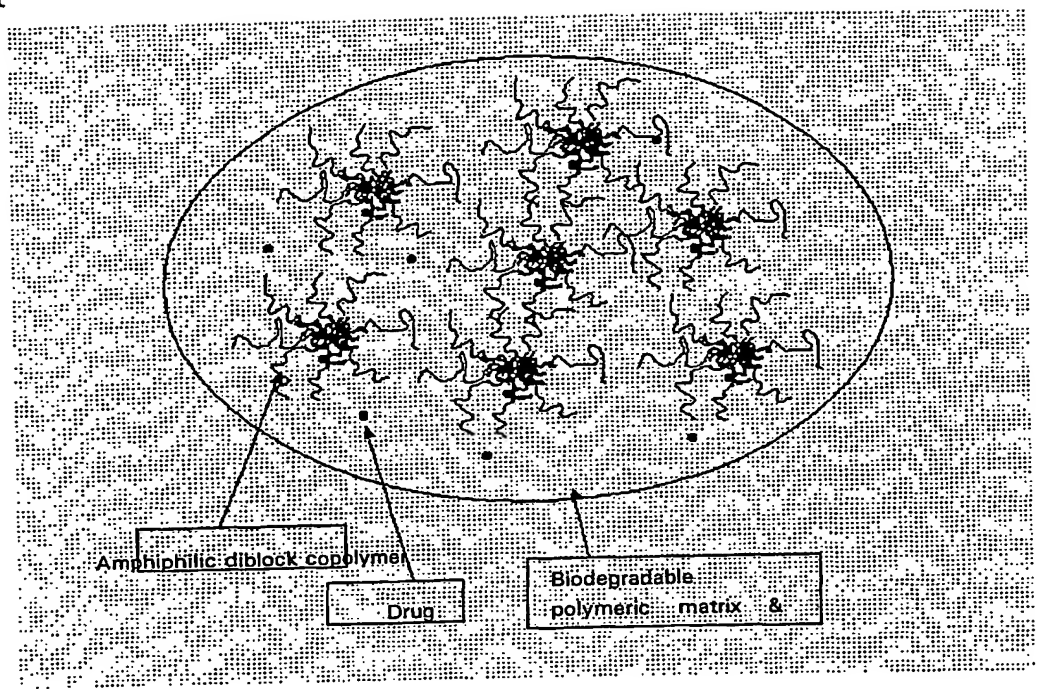

Amphiphilic diblock copolymer
Drug
Biodegradable polymeric matrix &

Fig. 2

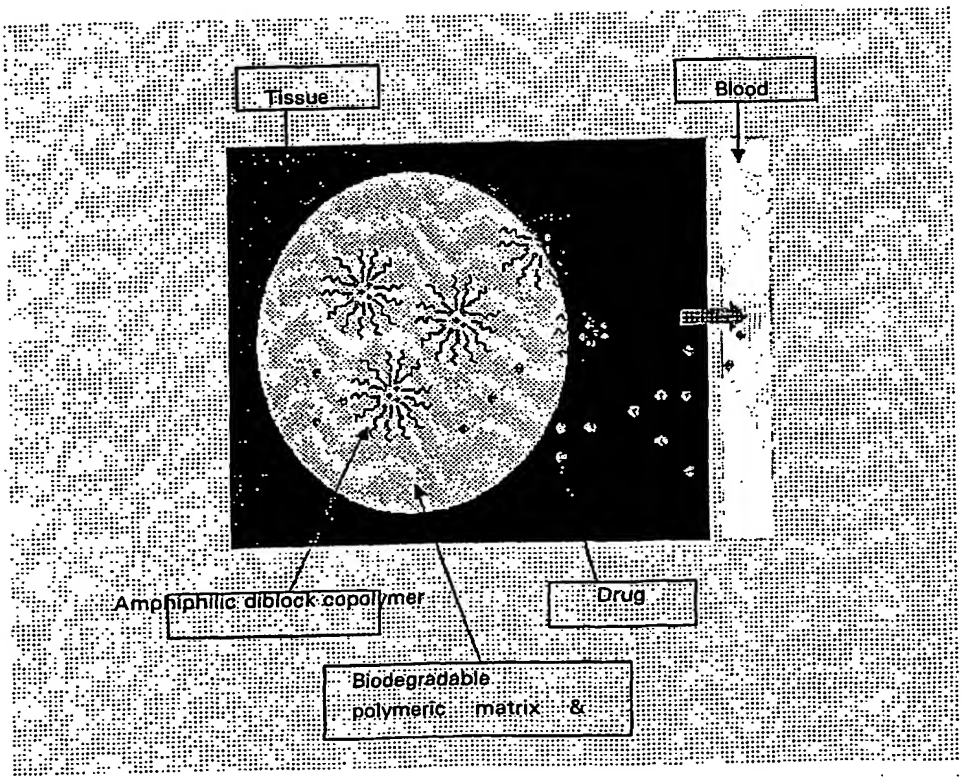
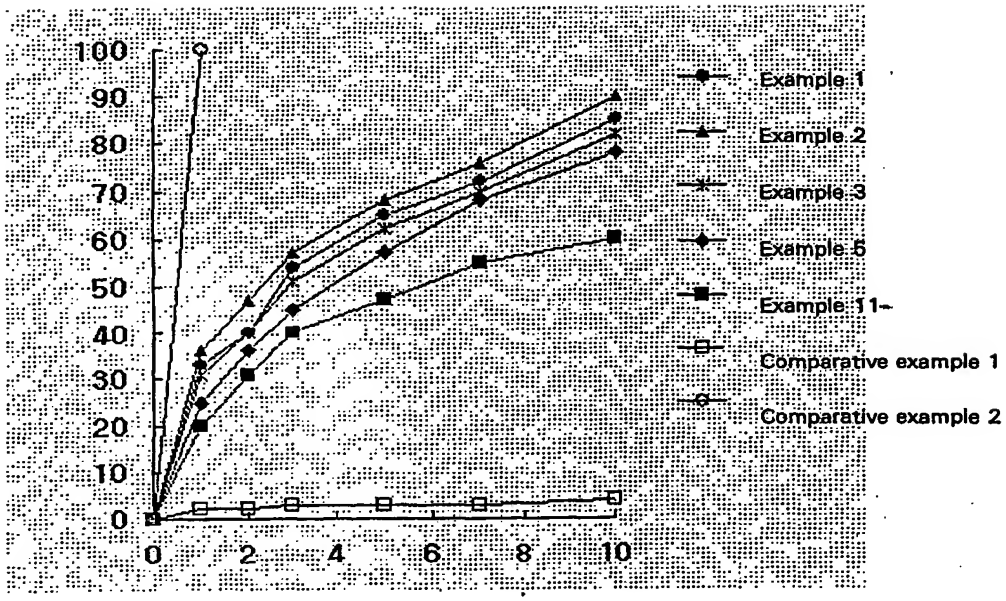

Tissue
Blood
Amphiphilic diblock copolymer
Drug
Biodegradable polymeric matrix &

Fig. 3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80
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60
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40
30
20
10
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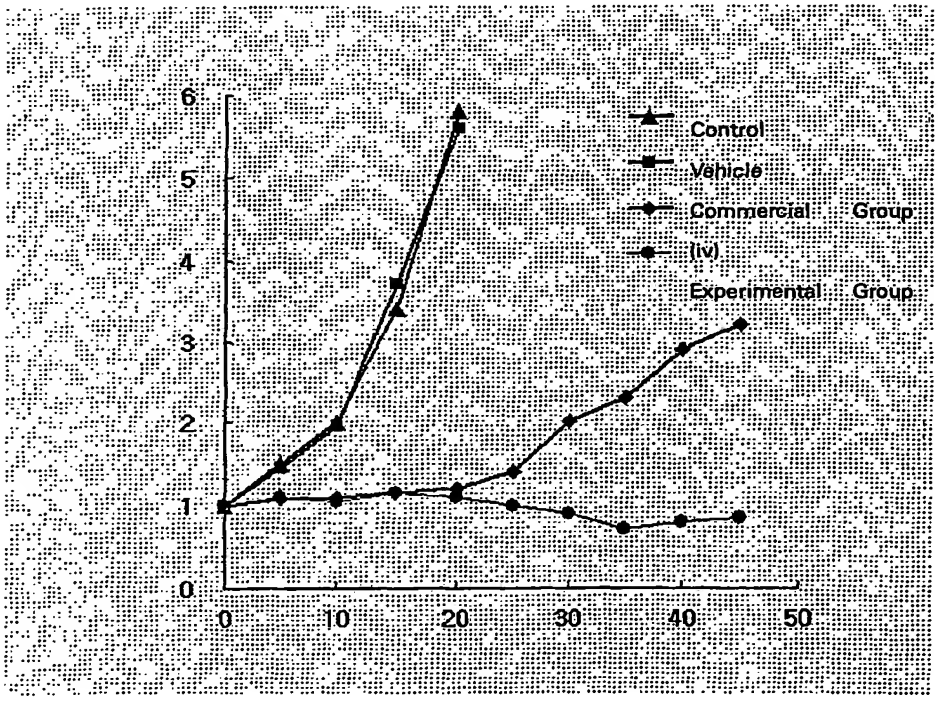
8
10
Example 1
Example 2
Example 3
Example 5
Example 11
Comparative example 1
Comparative example 2

Fig. 4


6
5
4
3
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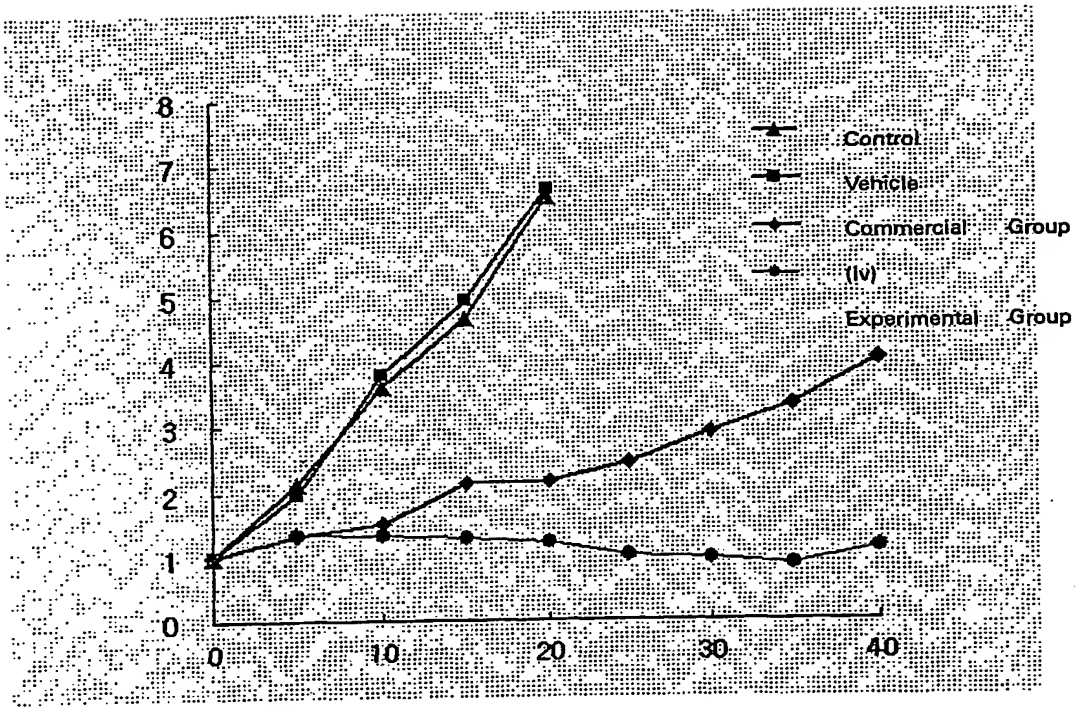
0
0
10
20
30
40
50
Control
Vehicle
Commercial Group
(iv)
Experimental Group

Fig. 5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Control
Vehicle
Commercial Group
(IV)
Experimental Group

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR01/02121

A. CLASSIFICATION OF SUBJECT MATTER

IPC7 A61K 9/127

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimun documentation searched (classification system followed by classification symbols)

IPC7: A61K

Documentation searched other than minimun documentation to the extent that such documents are included in the fileds searched

Electronic data base consulted during the internationl search (name of data base and, where practicable, search trerms used)

CA On-line

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, Y	WO 2001087345 A1 (SAMYANG Corporation) 22. November 2001 (22. 11. 2001) see the entire document.	1-15
P, Y	WO 2001085216 A1 (SAMYANG Corporation) 15. November 2001 (15. 11. 2001) see the entire document.	1-15
A	WO 9921908 A1 (ANGIOTECH PHARMACEUTICALS INC.) 06. May 1999 (06. 05. 1999) see the entire document.	1-15
A	Verrecchia et al., "Non-stealth (poly(lactic acid/albumin)) and stealth (poly(lactic acid-polyethylene glycol)) nanoparticles as injectable drug carriers" In J. Controlled Release (1995), 36(1-2), 49-61. see the entire document.	1-15

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 JANUARY 2002 (30.01.2002)	31 JANUARY 2002 (31.01.2002)

Name and mailing address of the ISA/KR	Authorized officer
Korean Intellectual Property Office Government Complex-Daejeon, 920 Dunsan-dong, Seo-gu, Daejeon Metropolitan City 302-701, Republic of Korea	Yoon, Kyung Ae
Facsimile No. 82-42-472-7140	Telephone No. 82-42-481-5609

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR01/02121

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9921908 A1	1999/05/06	AU 9896176 A1	1999/05/17